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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/530,207	02/13/2006	Mitsuo Oshimura	081356-0239	1647

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EXAMINER	
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ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Advisory Action Before the Filing of an Appeal Brief	Application No.	Applicant(s)	
	10/530,207	OSHIMURA ET AL.	
	Examiner	Art Unit	
	KEVIN K. HILL	1633	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 16 December 2009 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires *6* months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.
   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☒ The Notice of Appeal was filed on *16 December 2009*. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☒ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☒ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.
   NOTE: See *Continuation Sheet*. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☒ Applicant's reply has overcome the following rejection(s): See Continuation Sheet.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☒ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *18,20-22,26-28,33,37-46,49 and 50*.
   Claim(s) withdrawn from consideration: *1-17,23 and 51*.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: the amendment has not been entered.
12. ☐ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). _____
13. ☒ Other: See Continuation Sheet.

/Kevin K. Hill/
Examiner, Art Unit 1633

Continuation of 3. NOTE: The proposed amendment(s) to the claims add new limitations, thereby raising new issues which would require further search and consideration, e.g. the limitation "at AL163204", if the proposed amendment was entered.

Continuation of 5. Applicant's reply has overcome the following rejection(s): The prior rejection of Claims 41 and 46 under 35 U.S.C. 112, first paragraph, enablement, would be withdrawn in light of Applicant's proposed amendments to the claims.

Continuation of 13. Other:
Applicant argues that deletion of specific areas and keeping the remaining positions are crucial for obtaining a HAC vector which is capable of being transferred to human somatic cells, and of being retained stably in such cells. (See Specification Examples 4, 8, 14, 18, and 21-22). The Office's assertion that "Saffery et al taught that such centromere-proximal deletions is a routine design when engineering human minichromosome vectors" (Office Action, page 11) is incorrect because at the time the invention was made, human chromosome 21-based HACs were not stable in cells. There were technical difficulties in obtaining the stably retained human chromosome 21-based HAC as disclosed in the present application. Therefore, there was no reasonable expectation of success in finding the deletion positions as proposed. The Saffery reference itself describes the problems associated with the production of useful and stable HECs, e.g. their large size makes them difficult to manipulate to introduce genes and transfer intact from cell to cell, (Saffery pages 11-12). Thus, the references do not show that deletion of a distal region within the 21q11 region of the long arm and/or a distal region within the 21p11 region of the short arm of the human chromosome 21 could result in a stable HAC vector. Additionally, because of the large size of these vectors, one of skill in the art would not have known which region(s) of the HAC, if any, could be deleted to obtain a stable HAC. Deletion of a specific area of chromosome 21 creates a HAC vector that (1) can be stably transferred to human normal fibroblasts and to human normal somatic cells other than fibroblasts (see paragraph [0151] of US 2006/0185025) and (2) also is retained stably, for instance, in chicken cell lines and human cell clones (Examples 4 and 18) and in human stem cells (Examples 2 1 and 22), inter alia. Such is an unexpected result because, at the time the present invention was made, the prior art taught that human artificial chromosomes were not stable in mammalian cells. There was no suggestion or teaching in any of the referenced art that deletion of a distal region within the 21q11 region of the long arm and/or a distal region within the 21p11 region of the short arm of chromosome 21 would be capable of being transferred and retained stably in cells.
Applicant's argument has been fully considered, but is unpersuasive. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., stable HAC vector) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See In re Van Geuns, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). In the instant case, the claims do not require the method to yield HAC vectors that achieve Applicant's asserted unexpected result(s). Furthermore, Applicant appears to have overlooked that Kuroiwa et al (2000) taught mitotic stability of the HAC (pg 1087; Figure 4). Regarding the transfer of HACs from cell to cell, Kuroiwa et al and Tomizuka et al taught the routine ability of the ordinary artisan to transfer an HAC from cell to cell via microcells, for example. Thus, at the time of the invention, those of ordinary skill in the art would reasonably expect a human HAC comprising a deletion of a distal region within the 21q11 region of the long arm and/or a distal region within the 21p11 region of the short arm of the human chromosome 21 to functionally achieve a degree of mitotic stability, as such a chromosome would retain the hChr structural centromere comprising α-satellite DNA sequences having centromeric function.

Applicant argues that Hattori suggests nothing about deleting a distal region within the 21q11 region of the long arm and/or a distal region within the 21p11 region of the short arm of the human chromosome 21.
Applicant's argument has been fully considered, but is unpersuasive. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); In re Merck & Co., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In the instant case, Kuriowa et al (1998) teach a method for producing a human artificial chromosome vector and a method of introducing foreign DNA into a recipient cell, the methods comprising the step of obtaining donor cells that retain a human chromosome, deleting a distal region of the long arm and/or a distal region of the short arm of said human chromosome, wherein the deletion step is by substitution with an artificial telomere sequence. Similarly, Saffery et al taught strategies to produce a functional human artificial chromosome comprising the deletion of a distal region within the centromere-proximal region of the long arm and/or a distal region within the centromere-proximal region of the short arm of the human chromosome, whereupon the telomeric region either juxtaposes or is in close proximity to the α-satellite-based centromere. Tomizuka (1997) taught a successful method of producing hChr 2, 14 and 22 fragments and suggest the application of said method towards hChr21. Hattori et al taught the nucleotide sequence and annotation of human chromosome 21, achieving 99.7% coverage of 21q, within which AL163204 resides. Thus, at the time of the instantly asserted invention, those of ordinary skill in the art were aware of method of producing HACs comprising the deletion of a distal region within the centromere-proximal region of the long arm and/or a distal region within the centromere-proximal region of the short arm of the human chromosome, had sufficient motivation to perform said method on human chromosome 21, and possessed the structural and nucleotide sequence information of human chromosome 21 centromeres so as to appropriately design a specific telomere-truncation chromosome 21 vector comprising a specific insertion site of the recognition site for the site-specific recombination and a specific deletion of the region distal of the long and/or short arm of human chromosome 21 that retains one or more desired human chromosome 21 genes, and has removed one or more undesired human chromosome 21 genes so as to facilitate the study of the artisan's gene of interest.